



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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| <b>(51) International Patent Classification <sup>6</sup> :</b><br><b>A01N 29/04, 29/10, 31/00, 33/02, 35/00, 43/36, 43/40, A61K 31/03, 31/12, 31/13, 31/40, 31/44, 31/135, 31/435</b>   | <b>A1</b> | <b>(11) International Publication Number:</b> <b>WO 98/10647</b><br><b>(43) International Publication Date:</b> 19 March 1998 (19.03.98)   |
| <b>(21) International Application Number:</b> PCT/US96/14618<br><b>(22) International Filing Date:</b> 11 September 1996 (11.09.96)<br><br><b>(71)(72) Applicants and Inventors:</b> PLATT, Chris [US/US]; 14352 Riviera Street, Huntington Beach, CA 92647 (US). PLATT, Curtis [US/US]; 14352 Riviera Street, Huntington Beach, CA 92647 (US).<br><br><b>(74) Agent:</b> SCOTT, Gene; Patent Law & Venture Group, 2082 Business Center Drive #240, Irvine, CA 92612 (US).  |           | <b>(81) Designated States:</b> MX, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).<br><br><b>Published</b><br><i>With international search report.</i> |
| <b>(54) Title:</b> TOPICAL PREPARATION OF DIPHENHYDRAMINE AND HYDROCORTISONE TO TREAT DERMATITIS<br><br><b>(57) Abstract</b><br><br>A topical preparation for the treatment of dermatitis consisting of an antihistaminic chemical compound combined homogeneously with a chemical formulation containing at least one hydrocortisone compound. In the preferable embodiment, between 0-3 % diphenhydramine is combined with between 0-3 % hydrocortisone in a 4:3 weight ratio, with no more than 3 % of a hydrocortisone compound by volume of the preparation. |           |  |

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1 TITLE: TOPICAL PREPARATION OF DIPHENHYDRAMINE AND  
2 HYDROCORTISONE TO TREAT DERMATITIS

3  
4 **BACKGROUND OF THE INVENTION**

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6 **FIELD OF THE INVENTION:**

7 This invention relates generally to topical preparations for treating dermatitis  
8 and more particularly to a topical application consisting of a preferable 4:3 ratio of  
9 antihistamine diphenhydramine and anti-inflammatory hydrocortisone which  
10 increases the overall therapeutic effect of the preparation and treats many more types  
11 of dermatitis than available preparations.

12  
13 **DESCRIPTION OF PRIOR ART:**

14 Dermatitis is a superficial inflammation of the skin characterized by skin  
15 lesions and occasional itching and scratching. Most common forms of dermatitis are  
16 caused either by the presence of a noxious agent, such as insect bites and poison ivy  
17 (contact dermatitis), or by an immune reaction, such as urticaria (hives) and atopic  
18 dermatitis (allergic dermatitis). Other less common types of dermatitis include  
19 seborrhea, chronic dermatitis and dermatitis arising from immune deficiencies.

20  
21 Two distinct families of drugs have been found effective in the treatment of  
22 various types of dermatitis. Dermatitis due to bee stings, poison ivy or the presence  
23 of some other noxious agent is typically treated with an anti-itch and drying  
24 antihistamine, almost exclusively diphenhydramine. On the other hand, atopic and

1 other forms of dermatitis that are essentially immune reactions of the skin can only be  
2 effectively treated with an anti-inflammatory corticosteriod, typically, hydrocortisone,  
3 triamcinalone acetonide or betamethasone dipropionate.

4

5 Currently, the most widely used topical antihistamine preparations are  
6 Benadryl™ and Calamine™, which both use diphenhydramine as their active  
7 ingredient. Since neither preparation has significant side effects, they are available  
8 over the counter and are widely used.

9

10 Despite their popularity, the use of such topical antihistamines have  
11 significant weaknesses. The main problem associated with these preparations is that  
12 they have little or no transdermal efficiency, and are therefore incapable of treating  
13 the deeper layers of the skin, nor of curbing the redness or swelling of an infection.  
14 This is a significant deficiency for such preparations, as skin lesions are likely to  
15 grow in size if swelling and redness are not controlled.

16

17 The most popular available corticosteriod preparations are hydrocortisone  
18 cream or Cortaid™, triamcinalone or Kenalog™, and betamethasone or Valisone™.  
19 These steroids are well known for decreasing surface vasodilation and skin  
20 inflammation. Unfortunately, such treatments are also limited in that steroids cannot  
21 act as growth inhibitors or drying agents. In addition, stronger corticosteroids such as  
22 Kenalog™ and Valisone™ have serious toxic effects and are therefore limited in  
23 their use.

1  
2           However, the most profound disadvantage of both antihistamine and  
3 corticosteriod treatments arises from the fact that it is often initially impossible for  
4 physicians to distinguish between the different types of dermatitis. Since  
5 antihistamine preparations can only treat dermatitis caused by a noxious agent, and  
6 corticosteriod preparations can only treat dermatitis caused by immune reactions,  
7 neither type of preparation is capable of treating undiagnosed dermatitis with  
8 significant success. Instead of delaying treatment while further diagnosing and  
9 testing are completed, many general practitioners have become accustomed to simply  
10 prescribing a formulation of steroids and antimicrobials. However, while such a  
11 combination has proven effective with some types of dermatitis, there is still dispute  
12 as to whether a steroid/antimicrobial preparation has any effectiveness in atopic and  
13 contact dermatitis (Giannotti, et al., "Topical Steroids" Drugs: 44, 1992).

14  
15           The limitations of these prior preparations is particularly acute with over the  
16 counter treatments, as continued use of an inappropriate treatment allows lesions to  
17 continue to grow and spread unbeknownst to the user.

18  
19           Thus, there is a clear need for an improved topical preparation that can quickly  
20 and effectively treat all types of dermatitis. There is also a need for a preparation that  
21 increases absorption and decreases blood flow to the lesion without producing  
22 harmful side effects to the user. Such a preparation would provide all of the  
23 advantages of the prior art and incur none of the disadvantages. The present

invention fulfills these needs and provides further related advantages as described in the following summary.

#### **SUMMARY OF THE INVENTION**

The present invention is a topical preparation designed to effectively treat all types of common dermatitis without causing severe side effects. The present invention utilizes diphenhydramine, a common, proven antihistamine in combination with hydrocortisone, a mild steroid, in a 4:3 ratio. This formulation has been found, through a double-blind study, to have certain specific and desired advantages, most especially in the prescribed ratio.

At first glance, it appears that this combination does not constitute a new invention, as the benefits of both corticosteroid and antihistamine preparations in the treatment of dermatitis are well known to the public, as described above. In addition, hydrocortisone is a widely accepted anti-inflammatory steroid, and the key ingredient in the commercial anti-inflammatory Cortaid™, while diphenhydramine is the active ingredient in the well known topical antihistamine Benadryl™.

Still further, in the article entitled "Palliation of radiation-related mucositis," published in the February, 1990 issue of Special Care in Dentistry, Rothwell et al. teach a "shotgun" approach of multiple therapeutic agents which include the combination of hydrocortisone and diphenhydramine in an oral rinse. However, a closer look at the literature reveals that this formulation is to be used only to combat a

1 very rare form of mucositis, and, in fact, diphenhydramine is used as much for its  
2 unusual mucosal anesthetic qualities as for its antihistaminic properties.

3

4 And yet, despite its seeming obviousness, none of the prior art utilizes the  
5 present inventive combination of diphenhydramine and hydrocortisone. The reason  
6 for this is likely based on the fact that steroids typically tends to deactivate other  
7 active ingredients with which they are combined, hydrocortisone being no exception.

8

9 However, contrary to conventional thinking, our double blind tests found that  
10 a combination of hydrocortisone and diphenhydramine in a 4:3 ratio actually has  
11 synergistic benefits not otherwise predicted. In the proper 4:3 ratio, instead of  
12 deactivating the diphenhydramine, our tests found that the addition of hydrocortisone  
13 actually greatly increases the absorption rate of diphenhydramine, as the  
14 hydrocortisone acts as a carrier for the antihistaminic compound. Thus, the  
15 diphenhydramine is pulled deeper into the dermal layers where it can more quickly  
16 and effectively reduce the redness and treat dermatitis.

17

18 In the prescribed ratio, hydrocortisone also induces a time-release mechanism  
19 by encapsulating the diphenhydramine and causing it to be released over a longer  
20 period of time. This significantly reduces cases of persistent dermatitis in which the  
21 dermatitis periodically reoccurs. Still further, the compounding of the two substances  
22 causes the toxicity of the hydrocortisone to be greatly reduced, while still allowing it  
23 to reduce the swelling and improve the dermal penetration. This decreases any

1 harmful side effects and makes the preparation much more viable for over-the-counter  
2 purposes.

3

4 Thus, the present inventive combination is a significant improvement over all  
5 other prior art preparations. It combines two prevalent dermatitis-combating agents to  
6 provide a single preparation that can effectively treat both dermatitis caused by a  
7 noxious agent and by an allergic reaction. This provides for a much quicker treatment  
8 of both types of dermatitis with either over-the-counter or prescription preparations.  
9 With over-the-counter self-treatment, the present inventive preparation eliminates the  
10 common mismatching of medication and type of dermatitis, and with prescription  
11 medication, it eliminates the extended waiting period associated with diagnosing  
12 dermatitis type. Still further, the present inventive preparation introduces a  
13 compound with deeper penetration and time release features, making it much more  
14 effective at treating all types of dermatitis, not just a single type or cause.

15

16 These benefits, however, are greatly reduced as the ratio of the compound  
17 moves away from 4:3, thereby making the hydrocortisone/diphenhydramine  
18 combination an even less obvious decision. When the formula contains a greater  
19 portion of diphenhydramine, the compound tends to become oversaturated and  
20 ineffective, while with greater amounts of hydrocortisone, skin penetration of the  
21 compound is greatly reduced so that overall effectiveness is again, lessened.

22

23



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2

3 Other features and advantages of the present invention will become apparent  
4 from the following more detailed description which illustrates, by way of example,  
5 the principles of the invention.

6

7

### 8 **DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT**

9

10 The present invention is a topical preparation designed to treat the two most  
11 common types of dermatitis, both that caused by the presence of a noxious agent and  
12 that caused by an immune reaction. In essence, the preparation comprises an  
13 antihistaminic chemical compound combined homogeneously with a chemical  
14 formulation containing at least one hydrocortisone compound. Preferably, the  
15 antihistaminic compound is diphenhydramine, although the antihistaminic chemical  
16 compound could be any of the following chemical compounds including  
17 diphenhydramine hydrochloride, diphenhydramine compounds, chlorpheniramine  
18 maleate, triprolidine hydrochloride, cimetidine, brompheniramine maleate, clemastine  
19 fumarate, dexbrompheniramine maleate, pyrilamine maleate, pheniramine maleate  
20 and tripeleminamine hydrochloride. Likewise, the antihistaminic compound is  
21 preferably combined with hydrocortisone, although any hydrocortisone compound  
22 could be used including hydrocortisone acetate, and derivatives of hydrocortisone  
23 may also be used. However, for purposes of simplicity, the preparation is described

1 in its most preferable combination of diphenhydramine and hydrocortisone, although  
2 it is by no means limited to such agents.

3  
4 Not only does the present inventive combination of these two compounds  
5 effectively treat both common types of dermatitis but it also has synergistic benefits  
6 that are not otherwise expected by such a combination. Our studies have shown that  
7 hydrocortisone actually acts as a carrier for the diphenhydramine, pulling it more  
8 deeply through the skin and into the deep dermal layers where it is most effective.  
9 When hydrocortisone is combined with diphenhydramine, it also establishes a time-  
10 release mechanism so that the hydrocortisone and diphenhydramine are gradually  
11 released in the deep dermal layers over an extended period of time, thereby more  
12 effectively treating persistent dermatitis.

13  
14 After performing an extensive series of double blind studies, we have found  
15 an approximate 4:3 weight ratio of diphenhydramine/hydrocortisone is ideal for the  
16 present preparation, although the ratio can vary between 1:1 and 2:1 by weight and  
17 still retain some effectiveness. As the ratio of the two compounds moves away from  
18 the preferred 4:3 ratio, the effectiveness of the preparation rapidly drops. In larger  
19 ratios the preparation becomes over-saturated, and in lower ratios the preparation's  
20 penetration is severely limited.

21  
22 In addition, diphenhydramine and the other antihistaminic chemical  
23 compounds tend to be somewhat toxic and ineffective at high levels. Therefore, it is  
24 preferable to limit the weight ratios of the antihistaminic chemical compound in

1 relation to the overall weight of the preparation. The weight of the entire preparation  
2 should not be more than 3 percent of diphenhydramine, not more than 3 percent of  
3 diphenhydramine hydrochloride, not more than 3 percent of diphenhydramine  
4 compounds, not more than 4 percent of chlorpheniramine maleate, not more than 6  
5 percent of triprolidine hydrochloride, not more than 5 percent of cimetidine, not more  
6 than 4 percent brompheniramine maleate, not more than 5 percent of clemastine  
7 fumarate, not more than 5 percent of dexbrompheniramine maleate, not more than 5  
8 percent of pyrilamine maleate, not more than 5 percent of pheniramine maleate and  
9 not more than 6 percent of tripeleminamine hydrochloride.

10

11 Likewise, the hydrocortisone compound chemical formulation is preferably  
12 limited to not more than 3 percent by volume of the preparation.

13

14 While the invention has been described with reference to a preferred  
15 embodiment, it is to be clearly understood by those skilled in the art that the invention  
16 is not limited thereto. Rather, the scope of the invention is to be interpreted only in  
17 conjunction with the appended claims.

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## **CLAIMS**

What is claimed is:

1. A topical preparation for the treatment of dermatitis consisting of:  
a topical formulation including an antihistaminic chemical compound combined  
homogeneously with a chemical formulation containing at least one hydrocortisone  
compound.
2. The preparation of claim 1 wherein the hydrocortisone compound chemical  
formulation is not more than 3 percent by volume of the preparation and the weight  
ratio of the antihistaminic chemical compound and the hydrocortisone compound  
chemical formulation is between 1:1 and 2:1.
3. The preparation of claim 2 wherein the antihistaminic chemical compound is taken  
from the group of antihistaminic chemical compounds including diphenhydramine,  
diphenhydramine hydrochloride, diphenhydramine compounds, chlorpheniramine  
maleate, triprolidine hydrochloride, cimetidine, brompheniramine maleate, clemastine  
fumarate, dexbrompheniramine maleate, pyrilamine maleate, pheniramine maleate  
and tripelennamine hydrochloride.

1 4. The preparation of claim 3 wherein the hydrocortisone compound is taken from the  
2 group of hydrocortisone compounds including hydrocortisone, hydrocortisone  
3 acetate, and derivatives of hydrocortisone.

4

5 5. The preparation of claim 2 wherein the hydrocortisone compound is taken from the  
6 group of hydrocortisone compounds including hydrocortisone, hydrocortisone  
7 acetate, and derivatives of hydrocortisone.

8

9 6. The preparation of claim 2 wherein the antihistaminic chemical compound is taken  
10 from the group of weight limited antihistaminic chemical compounds including not  
11 more than 3 percent of diphenhydramine, not more than 3 percent of  
12 diphenhydramine hydrochloride, not more than 3 percent of diphenhydramine  
13 compounds, not more than 4 percent of chlorpheniramine maleate, not more than 6  
14 percent of triprolidine hydrochloride, not more than 5 percent of cimetidine, not more  
15 than 4 percent brompheniramine maleate, not more than 5 percent of clemastine  
16 fumarate, not more than 5 percent of dexbrompheniramine maleate, not more than 5  
17 percent of pyrilamine maleate, not more than 5 percent of pheniramine maleate and  
18 not more than 6 percent of tripeleminamine hydrochloride.

19

20 7. The preparation of claim 1 wherein the hydrocortisone compound chemical  
21 formulation is not more than 3 percent by volume of the preparation and the weight  
22 ratio of the antihistaminic chemical compound and the hydrocortisone compound  
23 chemical formulation is approximately 4:3.

1

2 8. The preparation of claim 7 wherein the antihistaminic chemical compound is taken  
3 from the group of antihistaminic chemical compounds including diphenhydramine,  
4 diphenhydramine hydrochloride, diphenhydramine compounds, chlorpheniramine  
5 maleate, triprolidine hydrochloride, cimetidine, brompheniramine maleate, clemastine  
6 fumarate, dexbrompheniramine maleate, pyrilamine maleate, pheniramine maleate  
7 and tripeleminamine hydrochloride.

8

9 9. The preparation of claim 8 wherein the hydrocortisone compound is taken from the  
10 group of hydrocortisone compounds including hydrocortisone, hydrocortisone  
11 acetate, and derivatives of hydrocortisone.

12

13 10. The preparation of claim 7 wherein the hydrocortisone compound is taken from  
14 the group of hydrocortisone compounds including hydrocortisone, hydrocortisone  
15 acetate, and derivatives of hydrocortisone.

16

17 11. The preparation of claim 7 wherein the antihistaminic chemical compound is  
18 taken from the group of weight limited antihistaminic chemical compounds including  
19 not more than 3 percent of diphenhydramine, not more than 3 percent of  
20 diphenhydramine hydrochloride, and not more than 3 percent of diphenhydramine  
21 compounds, not more than 4 percent of chlorpheniramine maleate, not more than 6  
22 percent of triprolidine hydrochloride, not more than 5 percent of cimetidine, not more  
23 than 4 percent brompheniramine maleate, not more than 5 percent of clemastine  
24 fumarate, not more than 5 percent of dexbrompheniramine maleate, not more than 5

- 1 percent of pyrilamine maleate, not more than 5 percent of pheniramine maleate and
- 2 not more than 6 percent of tripeleminamine hydrochloride.

3

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US96/14618**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) : Please See Extra Sheet.

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/277, 336, 340, 343, 408, 422, 638, 648, 678, 688, 691, 729, 751, 766

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

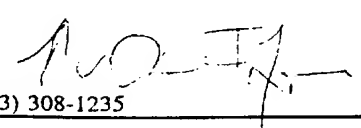
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**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|-----------------------|
| A         | BE, A, 682,828 (GILBERT) 31 August 1966, the entire document.                      | 1-11                  |
| A         | JP, A, 53-59,019 (LION HAMIGAKI K.K.) 27 May 1978, the entire document.            | 1-11                  |

☐ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

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| Date of the actual completion of the international search<br>10 OCTOBER 1996  | Date of mailing of the international search report<br>31 OCT 1996   |
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# INTERNATIONAL SEARCH REPORT

International application No.

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## A. CLASSIFICATION OF SUBJECT MATTER:

IPC (6):

A01N 29/04, 29/10, 31/00, 33/02, 35/00, 43/36, 43/40; A61K 31/03, 31/12, 31/13, 31/40, 31/44, 31/135, 31/435

## A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

514/277, 336, 340, 343, 408, 422, 638, 648, 678, 688, 691, 729, 751, 766